Remission Achieved with Tacrolimus in a Patient with ISN-RPS Class V Lupus Membranous Glomerulonephritis Unable to Tolerate Mycophenolate Mofetil

Ramy M. Hanna, MD, Marian Kaldas, MD and William D. Wallace, MD

Case Report

A 33-year-old Japanese American woman was admitted with facial swelling and diarrhea. She had multiple prior admissions to an outside hospital for presumed sinusitis. She was thought to have pan-colitis due to *Clostridium difficile*, but repeat testing was negative for *C. Diff* antigen. She had a history of hypothyroidism with positive markers for autoimmune Hashimoto’s Thyroiditis. Notably, there was no history of pregnancy loss, pre-eclampsia, or other thromboembolic events prior to her admission.

The patient had low complement levels (C3=23mg/dL, C4=4 mg/dL, CH50=13 mg/dL), positive anti-nuclear antibody at 1:1280 units homogenous pattern, and anti-ds DNA antibody of 344 IU/ml. These serological findings were suspicious for systemic lupus erythematosus. A pericardial effusion, pleural effusions, and a small pulmonary embolism were found on further testing. Alopecia, proteinuria, and severe hemolytic anemia (with decrease of hemoglobin to 6.7 g/dL) were also noted. The patient met definition for SLE disease activity using the newer SLICC criteria. Dilute Russel Viper Venom Time (DRVVT) and anti-cardiolipin antibody levels obtained before anticoagulation were non-conclusive and remained borderline after; therefore they were not diagnostic of antiphospholipid antibody syndrome. The DRVVT test initially showed no endpoint detected and was subsequently borderline on anticoagulation. Though, the anti-cardiolipin antibody IgA and IgG were negative when tested twice while the anti-cardiolipin IgM level was low level positive at 56.5 MPL and decreased to 21.6 MPL subsequently on anticoagulation therapy.

Initial renal workup was notable for severe proteinuria at 3.8-6.7 grams protein/gram creatinine. Her rivaroxaban anticoagulation for pulmonary embolism was held prior to renal biopsy. Two core biopsies with 12 total glomeruli were globally abnormal and showed sub-epithelial spikes with mild mesangial proliferation and sub-epithelial basement membrane deposits. The immunofluorescence showed positive “full house” capillary wall and mesangial staining for IgG (3-4+), IgA (1-2+), IgM (1-2+), C1q (3-4+), C3 (1-2+), and both light chains (1-2+). In total, the staging of the patient’s ISN-RPS Class V SLE membranous nephropathy was graded at stage II/IV without evidence of interstitial inflammation, crescent formation, or fibrosis. (See Figure 1).

The patient was placed on mycophenolate mofetil and high dose 1mg/kg prednisone during her initial admission. She was readmitted 2 months later with worsening proteinuria up to 13 grams of protein/gram creatinine on spot urine protein to creatinine ratio. The patient also continued to suffer from diarrhea despite antibiotic treatment and underwent extensive gastroenterological workup including esophagogastrroduodenoscopy and colonoscopy. After *Clostridium difficile* colitis was excluded she was felt to have the presumptive diagnosis of mycophenolate associated colitis. However, biopsy specimens showed only mild nonspecific interstitial infiltrates. A Cytomegalovirus (CMV) Polymerase Chain Reaction (PCR) in the blood was positive at 1,746 IU/ml and suggested another possible cause for her chronic diarrhea.

Nevertheless, the ongoing diarrhea in conjunction with the flare of LN necessitated new therapy. She was started on CMV treatment with valgancyclovir and tacrolimus dosage was modified with goal of a 12 hour trough level of 5-7 ng/ml. Her proteinuria immediately decreased and her hemolytic anemia resolved. Diarrhea resolved after treatment for CMV. The patient has continued to do well on warfarin anticoagulation, tacrolimus, and valgancyclovir. Her protein level decreased from a peak of 13 grams to a nadir of 0.4-0.6 grams/gram creatinine, achieving complete remission (defined as <0.5 grams protein/gram creatinine).
Her electrolytes and serum creatinine have remained at baseline, and anti-DS DNA antibody titers, which correlate with LN disease activity, have become undetectable. The patient has experienced no further clotting events on warfarin which remains therapeutic with very close monitoring. (See Figure 2).

**Discussion**

Systemic Lupus Erythematosus (SLE) is a devastating disease that can target various organ systems including the nervous system, heart, lungs, hematopoietic system, and kidneys. Variation in the disease of lupus range from cutaneous-only manifestations to severe life threatening disease such as lupus cerebritis or coagulopathy including catastrophic antiphospholipid antibody syndrome, and end stage renal disease from rapidly progressive diffuse proliferative glomerulonephritis. The pathophysiology behind SLE is due to loss of tolerance to immune system and the upregulation of some interferons. Variation in the disease of lupus range from cutaneous-only manifestations to severe life threatening disease such as lupus cerebritis or coagulopathy including catastrophic antiphospholipid antibody syndrome, and end stage renal disease from rapidly progressive diffuse proliferative glomerulonephritis. The classification is based on the location and intensity of the immune complex deposits and the degree of glomerular changes. The mildest manifestation of disease is minimal mesangial (class I) or mesangial (class II) lupus nephritis. Focal proliferative and diffuse proliferative glomerulonephritis (FPGN and DPGN) are the more severe forms of active disease (Class III and IV, respectively). These are due to sub-endolothelial deposits, in class III LN, the changes affect less than 50% of glomeruli and in class IV, the glomerular changes affect greater than 50% of glomeruli. Class V LN represents sub-epithelial immune complex deposition and is called membranous lupus nephritis. This is a distinct pathological entity and tends to present with sub-epithelial glo merular basement membrane spikes and is more commonly nephrotic rather than nephritic in presentation. Treatment has tended to be with mycophenolate mofetil or mycophenolic acid, though other alternatives can be considered in lupus nephritis. The antiCD20 monoclonal antibody Rituxamab and the calcineurin inhibitor (CNIs) have been used as adjunct/alternative treatments in this LN in the proliferative types of LN subtype as well this subtype. Class VI lupus nephritis represents end stage renal disease and is defined as greater than 90% glomerulosclerosis. This patient with severe active lupus nephritis and severe nephrotic syndrome with proteinuria was unable to tolerate the standard therapy for LN including type V membranous glomerulonephritis due to SLE. However, the patient was able to tolerate the dosing of 2 mg of tacrolimus in AM and 1.5 mg of tacrolimus in PM and maintained through levels between 5 and 7 ng/ml with resulting control of proteinuria and great diminishing of SLE disease activity. Her dose is the current recommended dose for tacrolimus used to treat refractory SLE nephritis. It is interesting her serum creatinine came up slightly with tacrolimus use but given how stable her levels have been between 5-7 we feel this is possibly also likely to her kidneys no longer hyper-filtering with the dramatic decrease in proteinuria (please see Figure 2). She remains in complete remission on this alternate treatment.

This supports the efficacy of calcineurin inhibitors (CNIs), widely used transplant immune-suppressants, in controlling SLE disease activity including LN. This option should be considered as a second or third line agent in LN, but especially in class V membranous GN. Many studies have shown similar successes with use of CNIs in primary membranous nephropathy with less toxicity than the traditional alternatives (corticosteroids and cyclophosphamide). It is important to consider the risk of CNI toxicity, including renal vascular disease, and risk of relapse of SLE membranous LN once CNIs are stopped. Rituxamab may also be a useful adjunctive treatment in primary membranous nephropathy though it is also being tested in LN generally and Class V membranous LN as well.
REFERENCES


Submitted April 12, 2018